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Reply

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preliminary studies of an animal model of ehrlichiosis [8]. Immunoblots of sera from Balb/C mice experimentally infected with *Ehrlichia microti*, but not *B. burgdorferi*, demonstrated reactivity to OspC, OspA, 36, 38, 93 kDa, and other antigens [8].

Contrary to the assertion of Günthard et al., a negative serology for *Ehrlichia equi* does not exclude coinfection with *Ehrlichia*. We have seen seronegative patients for whom the clinical diagnosis was supported in other ways (e.g., cultures). These authors did not report the results of a culture for *Ehrlichia* or of a PCR assay. Conclusions concerning the sensitivity of serology for *E. equi* in the diagnosis of HGE (for both doxycycline-treated patients and untreated patients) should not be drawn until more data become available.

Leukopenia and thrombocytopenia are common findings in patients with ehrlichiosis [9] and have been observed in 71% of Slovenian patients during the initial phase of tick-borne encephalitis [10]. Babesiosis is also known to cause these hematologic abnormalities. Any of these three illnesses could have coexisted with *B. burgdorferi* infection [9] in the patient of Günthard et al. Case reports such as theirs should serve as an impetus to study the prevalence of HGE and babesiosis in those parts of Europe where *Ixodes* ticks are already known to be vectors for *B. burgdorferi* and the tick-borne encephalitis virus.

We are concerned that the addition of another protean manifestation of Lyme borreliosis, based on anecdotal evidence, will contribute to the growing mythology surrounding this illness. Where possible, microbiological confirmation by culture should be used to define the spectrum of *B. burgdorferi* infections [2, 3], particularly when atypical manifestations are present. The clinical manifestations of coinfection with *B. burgdorferi* and the agents of HGE, babesiosis, or tick-borne encephalitis virus have yet to be defined. Until more solid evidence to the contrary appears, we will assume that if a patient with Lyme borreliosis has leukopenia or thrombocytopenia, these hematologic abnormalities are due to an etiology other than infection with *B. burgdorferi* (e.g., coinfection with HGE).

This issue is not merely of academic interest but is pertinent to the choice of antibiotic in the treatment of Lyme borreliosis. Although tetracyclines and some β -lactam antibiotics are useful for treating *B. burgdorferi* infection, only tetracyclines are clearly effective in the treatment of HGE and thus should be prescribed (as Günthard, et al. did) for patients with possible dual infection.

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References

- Günthard HF, Péter O, Gubler J. Leukopenia and thrombocytopenia in a patient with early Lyme borreliosis. *Clin Infect Dis* 1996;22:1119–20.
- Strle F, Nelson JA, Ruzic-Sabljic E, et al. European Lyme borreliosis: 231 culture-confirmed cases involving patients with erythema migrans. *Clin Infect Dis* 1996;23:61–5.
- Nadelman RB, Nowakowski J, Forseter G, et al. The clinical spectrum of early Lyme borreliosis in patients with culture-confirmed erythema migrans. *Am J Med* 1996;100:502–8.
- Kamp T, Zink C, Beer C, Kaboth W, Nerl C. Agranulozytose durch infektiös-toxische Knochenmarkschädigung nach Borrelien-Infektion. *Dtsch Med Wschr* 1995;120:636–40.
- Goellner MH, Agger WA, Burgess JH, Duray PH. Hepatitis due to recurrent Lyme disease. *Ann Intern Med* 1988;108:707–9.
- Schwartz I, Wormser GP, Schwartz JJ, et al. Diagnosis of early Lyme disease by polymerase chain reaction amplification and culture of skin biopsies from erythema migrans lesions. *J Clin Microbiol* 1992;30:3082–8.
- Wormser GP, Horowitz HW, Dumler JS, Schwartz I, Aguero-Rosenfeld M. False-positive Lyme disease serology in human granulocytic ehrlichiosis. *Lancet* 1996;347:981.
- Hofmeister EK, Magera J, Sloan L, Kolbert C, Hanson J, Persing DH. *Borrelia burgdorferi* proteins are recognized by antibodies from mice experimentally infected with the agent of human granulocytic ehrlichiosis [abstract E814]. In: Program and abstracts of the 7th International Congress on Lyme Borreliosis (San Francisco). 1996.
- Pancholi P, Kolbert CP, Mitchell PD, et al. *Ixodes dammini* as a potential vector of human granulocytic ehrlichiosis. *J Infect Dis* 1995;172:1007–12.
- Lotrič-Furlan S, Strle F. Thrombocytopenia—a common finding in the initial phase of tick-borne encephalitis. *Infection* 1995;23:203–6.

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Reply

SIR—Nadelman and colleagues comment that although much of the clinical presentation of our patient was compatible with North American Lyme borreliosis, it was not typical of the cases seen in Slovenia. It was not our intention to report a usual clinical presentation of European Lyme borreliosis. Strle et al. [1] have reported that 13%–17% of the tick isolates of *Borrelia* in Slovenia have been *B. burgdorferi* sensu stricto, the same species most commonly found in the United States. Thus, clinical presentations similar to those described in the United States may be observed in Europe, although less frequently. For example, in our region we see patients with multiple erythema migrans, an unusual finding in European patients, and we have found that almost 50% of tick isolates of *Borrelia* in our region have been found to be *B. burgdorferi* sensu stricto [2].

Nadelman and colleagues seem to have doubts about our diagnosis of Lyme borreliosis. However, the following findings make us confident of the diagnosis. First, the expanding lesion in our patient was a classic erythema migrans. Second, we observed a typical seroconversion with the screening ELFA (enzyme linked fluorescent assay) VIDAS Lyme IgG + IgM (bioMérieux, Marcy l'Etoile, France). Third, these results were confirmed by an immunoblot assay, which

at first showed a strong reaction to flagellin, accompanied by a few others (to p39 in particular); these reactions were followed by a strong reaction to OspC, which is typically seen in early borrelia infections, and finally by a complete reaction to >10 antigens of *Borrelia*. These findings fulfilled the Centers for Disease Control and Prevention criteria for a positive IgG and IgM immunoblot assay.

If this strong reactivity to *Borrelia* had been caused by cross-reactivity to *Ehrlichia*, we would have expected to detect antibodies to *E. equi* or *E. phagocytophila*, the *Ehrlichia* species probably transmitted by *Ixodes ricinus* in Switzerland [3]. The two reports that Nadelman et al. referred to [4, 5] showed that all patients or mice with ehrlichiosis developed antibodies to *Ehrlichia* antigens, as determined by indirect immunofluorescence assay, and then showed cross-reactivity to *B. burgdorferi* in an ELISA with equivocal immunoblots.

We agree with Nadelman and colleagues that leukopenia, thrombocytopenia, and elevated liver enzyme levels are common features in human ehrlichiosis. This is the reason we sent one serum sample each (21 and 90 days, respectively, after the beginning of our patient's symptoms) to two reference laboratories working with *Ehrlichia*. Neither sample showed antibodies to *E. equi* or *E. phagocytophila*.

Of course, we are aware of the wide range of pathogens transmitted by *I. ricinus* [6–8]. The other possible pathogens were excluded by multiple negative serologies for tick-borne encephalitis as well as by the setting in which the infection occurred and by the clinical presentation of our patient.

In conclusion, we have nearly ruled out ehrlichiosis and tick-borne encephalitis and clearly confirmed early Lyme borreliosis in our patient.

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References

1. Strle F, Cheng Y, Nelson JA, Picken MM, Bouseman JK, Picken RN. Infection rate of *Ixodes ricinus* ticks with *Borrelia afzelii*, *Borrelia garinii*, and *Borrelia burgdorferi* sensu stricto in Slovenia. *Eur J Clin Microbiol Infect Dis* 1995;14:994–1001.
2. Péter O, Bretz AG, Bee D. Occurrence of different genospecies of *Borrelia burgdorferi* sensu lato in ixodid ticks of Valais, Switzerland. *Eur J Epidemiol* 1995;11:463–7.
3. Pfister K, Roesti A, Boss PH, Balsiger B. *Ehrlichia phagocytophila* als Erreger des Weidefiebers im Berner Oberland. *Schweiz Arch Tierheilkd* 1987;129:343–7.
4. Wormser GP, Horowitz HW, Dumler JS, Schwartz T, Aguero-Rosenfeld M. False-positive Lyme disease serology in human granulocytic ehrlichiosis [letter]. *Lancet* 1996;347:981.
5. Hofmeister EK, Magera J, Sloan L, Kolbert C, Hanson J, Persing DH. *Borrelia burgdorferi* proteins are recognized by antibodies from mice experimentally infected with the agent of human granulocytic ehrlichiosis [abstract E814]. In: Program and abstracts of the 7th International Congress on Lyme Borreliosis (San Francisco). 1996.
6. Aeschlimann A, Burgdorfer W, Matile H, Péter O, Wyler R. Aspects nouveaux du rôle de vecteur joué par *Ixodes ricinus* L. en Suisse. *Acta Trop (Basel)* 1979;36:181–91.
7. Péter O, Williams JC, Burgdorfer W. *Rickettsia helvetica*, a new spotted fever group rickettsiae: immunochemical analysis of the antigens of 5 spotted fever group rickettsiae. In: Proceedings of the 3rd International Symposium on Rickettsiae and Rickettsial Diseases (Smolenice), Slovakia. Bratislava, Slovakia: Slovak Academy of Sciences, 1984;99–108.
8. Burgdorfer W, Barbour AG, Hayes SF, Péter O, Aeschlimann A. *Erythema chronicum migrans*—a tickborne spirochetosis. *Acta Trop (Basel)* 1983;40:79–83.

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